Remarks

The Rejection of Claims 32 and 56-58 Under 35 U.S.C. § 112, first paragraph

Claims 32 and 56-58 stand rejected under 35 U.S.C. § 112, first paragraph as lacking written description for the recitation "antigenic peptide(s)."[1] Dependent claims 32 and 56-58 recite that an identical antigenic peptide is bound to each ligand binding site recited in independent claim 28. The Office Action asserts that the written description requirement for the genus of antigenic peptides can be satisfied only by a disclosure of specific molecules. Office Action mailed August 8, 2005 at pages 2 and 3. This assertion is not consistent with well-established legal precedent.

The specification preferably does not describe what is known in the art. *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). *See also* M.P.E.P. § 2163(II)(A)(3)(a) ("[t]he description need only describe in detail that which is new or not conventional in the art.") and the Revised Interim Written Description Guidelines Training Materials at page 4. Rather, the existing knowledge in a particular field, the extent and content of the prior art, and the maturity of the science at issue must be considered when determining what is needed to support generic claims to biological subject matter. *Capon v. Eshhar*, 418 F.3d 1349, 1359, 76 U.S.P.Q. 2d 1078, 1085 (Fed. Cir. 2005).

"Antigenic peptides" are neither new nor unconventional in the art. They do not require explicit description to be understood by those skilled in the art. See Applicants' response filed March 8, 2005 at pages 2-4.

The rejection is legally incorrect. Applicants respectfully request its withdrawal.

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[1] The rejection refers to claims "52-58" but this appears to be a typographical error. "Antigenic peptides" are recited only in claims 32 and 56-58.

The Rejection of Claims 28-31 and 51-55 Under 35 U.S.C. § 103(a)

Claims 28-31 and 51-55 stand rejected under 35 U.S.C. § 103(a) as obvious over Matsui[2] in view of Dal Porto,[3] Chang,[4] and Harris.[5] Applicants respectfully traverse the rejection.

To determine whether an invention is obvious, the invention must be considered as a whole. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1537, 218 U.S.P.Q. 871, 877 (Fed. Cir. 1983). Independent claim 28 is directed to a composition comprising a cell with a molecular complex bound to its surface. The molecular complex comprises at least two of each of two types of fusion proteins. One fusion protein comprises an immunoglobulin heavy chain, wherein the immunoglobulin heavy chain, including the variable region, and an extracellular portion of a first transmembrane polypeptide. The other fusion protein comprises an immunoglobulin light chain and an extracellular portion of a second transmembrane polypeptide. The molecular complex comprises two ligand binding sites, which are formed by the extracellular domains of the first and second transmembrane polypeptides.

The burden of establishing that the claimed compositions are *prima facie* obvious rests with the Examiner. The *prima facie* case requires a showing that the cited prior art teaches or suggests all the claim limitations. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. 8th ed., § 2142. The *prima facie* case also requires a showing that one of ordinary skill would have been motivated to combine the cited references. *In re Linter*, 458 F.2d 1013, 1016,

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[2] Matsui *et al.*, *Proc. Natl. Acad. Sci. U.S.A. 91*, 12862-66, December 1994.

[3] Dal Porto *et al.*, *Proc. Natl. Acad. Sci. U.S.A. 90*, 6671-75, 1993.

[4] Chang *et al.*, *Proc. Natl. Acad. Sci. USA 91*, 11408-412, 1994.

[5] Harris *et al.*, WO 94/09131, April 28, 1994.

173 U.S.P.Q. 560, 562 (C.C.P.A. 1972). The cited references must be considered in their entireties, including portions that would have led the ordinary artisan away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 U.S.P.Q. 303, 310 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The Office Action does not consider the claimed invention as a whole and has not considered the entirety of any of the references. When properly analyzed, the cited prior art does not render any of claims 28-31 and 51-55 *prima facie* obvious.

The Office Action cites the primary reference, Matsui, as teaching that "the interaction between monovalent TCRs and MHC heterodimers has been difficult to study directly due to the very low affinity." Office Action at page 5, par. 1 (quoting the abstract of Matsui). The Office Action contends that this teaching would have motivated one of ordinary skill to produce "a high affinity divalent TCR/IgG and class II MHC/IgG molecules [sic] . . . ." Office Action at page 9, lines 4-6. This contention does not take into account the teachings of Matsui as a whole and ignores a specific teaching in Matsui that would have led the ordinary artisan away from the claimed compositions.

Matsui addresses the problem of how to obtain direct measurements of TCR-peptide/MHC binding kinetics under various conditions. Matsui acknowledges that soluble TCRs are available and that several studies had determined the affinity of soluble TCR binding to a soluble peptide/MHC to be relatively low (K_d of 4-6 x 10^{-5} M, 10^{-4}-10^{-7} M, and 10^{-5} M, respectively). Matsui points out that these measurements were indirect and, further, explicitly states that their dependence on using live cells was a disadvantage:

> However, none of these studies give direct information about the kinetics of the molecular interactions and are dependent on live

> cells, thus greatly limiting the range of conditions (temperature, ionic strength, etc.) that can be assessed.

Matsui at page 12862. Matsui teaches use of surface plasmon resonance to overcome the disadvantages of cell-based indirect measurements. The surface plasmon resonance measurements were conducted in "a completely cell-free, aqueous system" with the soluble TCR immobilized in a specialized BIACORE® flow cell. Matsui at page 12865, col. 1.

In contrast, the pending claims recite a molecular complex bound to the surface of a cell. The limitations of using a cell-bound TCR are exactly what Matsui sought to overcome. Matsui thus explicitly teaches away from cell surface binding. This alone is sufficient to defeat a *prima facie* case of obviousness. Moreover, Matsui as a whole would not have motivated one of ordinary skill to seek "high affinity divalent TCR/IgG and class II MHC/IgG molecules" as the Office Action contends. Matsui provides a method by which low affinity TCR-peptide/MHC interactions can be studied directly. Matsui contains no suggestion that the affinity of these molecules should be modified.

None of the secondary references, either alone or in combination, make up for the deficiencies of Matsui. Nor would one of ordinary skill have been motivated to combine their teachings. Harris teaches recombinant proteins with two binding regions. The Office Action cites Harris as demonstrating "that binding domains can be fused via a linker to the N-terminus of the variable regions of immunoglobulin heavy and light chains without altering the binding function of the fusion proteins." Office Action at page 8, last 3 lines. However, the Office Action ignores teachings of Harris that would have led away from the claimed invention. Although Harris teaches that immunoglobulin domains can be used to associate the two binding

regions, it explicitly teaches away from using an immunoglobulin heavy chain, which Harris teaches has undesirable effector functions:

> Bivalent antibodies of a monospecific nature may be derived from hybridomas and similarly, bispecifics by the fusion of two hybridoma lines expressing antibodies with different specificities. However, using this strategy, the application of bispecifics has been limited by the difficulty in efficiently producing and purifying such molecules and additionally, the effector functions intrinsic to complete antibody molecules (such [as] Fc receptor and complement binding) have led to undesirable interactions.

Harris, paragraph bridging pages 1 and 2, emphasis added.

Chang teaches a method of making a soluble TCR using a leucine zipper to overcome the obstacle of inefficient pairing of TCR α and β subunits. The Office Action cites Chang as teaching that "fusion of peptide sequences known to form unique heterodimeric coiled-coils to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over homodimer formation" and that such coiled-coils could be used to associate any type of heterodimeric structure. Office Action at page 8.

Chang, even in combination with Harris and Matsui, would not have led one of ordinary skill to make a molecular complex using an immunoglobulin molecule. Polypeptides associated via a leucine zipper are stabilized by interdigitation of leucine residues on two protein alpha-helices. In contrast, all domains of immunoglobulin chains contain two layers of β-pleated sheet which have three or four strands of antiparallel polypeptide chain, and the immunoglobulin chains are held together with disulfide bonds.[6] Chang's teaching of leucine zippers would not have motivated an ordinary artisan to use immunoglobulin chains.

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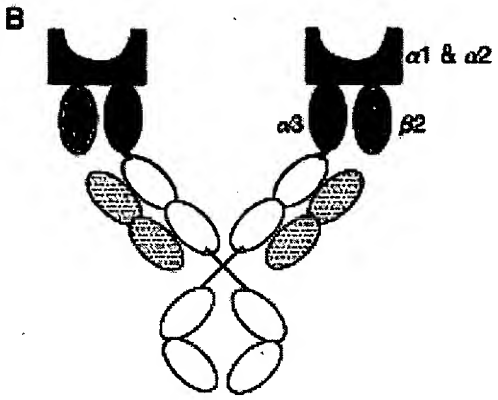
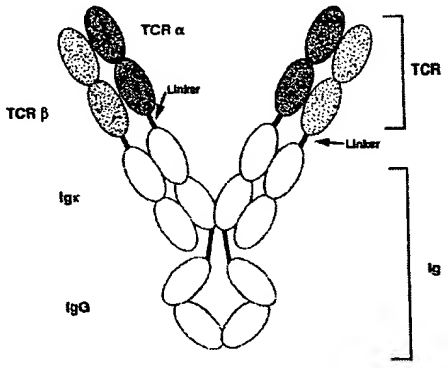
[6] Abbas *et al.*, eds., Cellular and Molecular Immunology, 3d ed., pages 41-43 (attached).

Finally, the Office Action cites Dal Porto as disclosing divalent class I MHC/IgG molecules which have nanomolar affinity for T cell receptors and, in contrast to monovalent MHC class I molecules, can inhibit lysis of target cells. Office Action at page 7. Dal Porto teaches a molecule which differs substantially from the recited molecular complex. The molecule of Dal Porto (left; Fig. 1B) and one embodiment of the recited molecular complex (right; specification Fig. 1D) are illustrated below.



Dal Porto, Fig. 1B



specification, Fig. 1D

Dal Porto's molecule is a class I MHC/IgG molecule which comprises (1) an immunoglobulin molecule comprising two heavy chains and two light chains and (2) two MHC class I molecules, each comprising an α chain and a β_2 microglobulin subunit. Each of the two immunoglobulin heavy chains is fused to an α chain of a class I MHC molecule. Neither the light chains nor the β_2 microglobulin subunits are part of a fusion protein. The β_2 microglobulin subunit simply associates with the α chain as it normally does in a native class I MHC molecule. Thus, Dal Porto's complexes comprise a single species of fusion protein which consists of the immunoglobulin heavy chain and the MHC class I α chain.

In contrast, the recited molecular complexes comprise two different fusion proteins. One fusion protein comprises an immunoglobulin heavy chain and an extracellular portion of a first

transmembrane polypeptide. The other fusion protein comprises an immunoglobulin light chain and an extracellular portion of a second transmembrane polypeptide. Both of these two fusion proteins are different from the single fusion protein of Dal Porto. Thus, modifying Dal Porto's molecule to arrive at a molecular complex such as that illustrated above would have involved two modifications: (1) fusing the extracellular domain of a first transmembrane polypeptide to the immunoglobulin heavy chain in place of the class I MHC α chain and (2) fusing the extracellular domain of a second transmembrane polypeptide to the immunoglobulin's light chain. Dal Porto does not teach or suggest either of these modifications.

In fact, those of skill in the art at the April 28, 1996 priority date of this application knew that no particular manipulation was needed to cause the extracellular domains of MHC class II molecules or TCRs to associate to form functional peptide binding sites. It was well known that the two extracellular domains of TCR molecules or of class II MHC molecules will associate to form a peptide binding site in the absence of their transmembrane domains. That is, the ordinary artisan knew that one extracellular domain need not be anchored in any particular orientation relative to the other extracellular domain in order for the two extracellular domains to associate and form a functional peptide binding site.

For example, U.S. Patent 5,723,309 discloses soluble TCR molecules which contain the extracellular domains but not the transmembrane domains of each polypeptide chain: "VγCγ/VδCδ soluble T receptors are also produced by co-transfecting, into a host cell, DNA sequences encoding the γ and δ submits [sic; subunits] of the Tγδ receptor from which the transmembrane portion of the Tγδ receptor has been deleted." Col. 2, lines 48-51. When the transfected DNA is expressed, a soluble TCR containing both extracellular domains is secreted into the supernatant: "[T]he soluble γδ hetero-dimers were clearly detected by IRMA

(radioimmunological assay) in the supernatants of CHO cells co-transfected with soluble γ and soluble δ assembly products (γδsFS-CHO) when pairs of antibodies specific for Vδ2/Cγ or Vδ2/Vγ9 were used" Col. 8, lines 43-50. The soluble TCR molecules contain a functional peptide binding site and can be used diagnostically (col. 5, lines 3-13) and therapeutically (col. lines 57-60).

U.S. Patent 5,583,031 discloses a soluble class II MHC molecule that contains extracellular domains of each polypeptide chain but not the transmembrane domains and that can bind an antigenic peptide:

> Class II histocompatibility proteins are expressed as αβ heterodimers by insect cells (*Spodoptera frugiperda*, fall armyworm) infected with recombinant baculoviruses. The viruses carry genes coding for the α and for the β subunits of the histocompatibility protein. The protein can be produced in a membrane-associated form, or in a secreted, soluble form by alteration of the carboxy-terminus. Like the mammalian cells from which histocompatibility proteins are conventionally isolated, the insect cells glycosylate and correctly assemble the histocompatibility protein, but, unlike the mammalian cells, they do not load the binding site with tightly bound endogenous peptides. The proteins are isolated from insect cells as empty molecules by immunoaffinity and ion-exchange procedures. Antigenic peptide is loaded onto the purified molecule in vitro, and the 1:1 complex of peptide and histocompatibility protein is isolated.

Col. 5, lines 9-24.

As evidenced by these two patents, the ordinary artisan would not have thought that any particular manipulation was necessary to permit the extracellular domains of TCRs or class II MHC molecules to associate. Even if, *arguendo*, one of ordinary skill had been motivated to modify Dal Porto's divalent MHC class I/IgG molecule to make a divalent TCR/IgG or class II MHC/IgG molecule, the logical approach would have been to express one extracellular domain

as a fusion protein with the immunoglobulin heavy chain, express the other extracellular domain by itself, and permit the two extracellular domains to associate as the prior art taught they would. But this method would not form the present invention. To form the present invention, the second extracellular domain must be fused to the immunoglobulin light chain. None of the prior art motivates the ordinary artisan to make this modification of Dal Porto's molecule. There would have been no motivation for the ordinary artisan to take the extra step of fusing one of the extracellular domains to the immunoglobulin light chain.

The cited prior art references, when properly considered in their entireties, do not make claims 28-31 and 51-55 *prima facie* obvious. The claims require a cell to which is bound the recited molecular complex. None of the cited references teaches or suggests the recited molecular complex or binding it to the surface of a cell. Matsui teaches away from cell surface binding and does not suggest construction of any molecules with higher binding affinities. Harris teaches away from using an immunoglobulin heavy chain. Chang teaches use of polypeptides with different structural properties than immunoglobulin chains to associate extracellular TCR domains. Dal Porto teaches a molecule with a structure that substantially differs from the molecular complex recited in the pending claims. One of ordinary skill would not even have been motivated to combine these references, much less make the extensive modifications necessary to make the present invention. Nor do the cited references, even if combined, lead one of ordinary skill to use the cells in a pharmaceutical composition (claim 31) or to bind identical antigenic peptides to each ligand binding site of the complex (claims 32, 56, and 57).

The PTO has used the specification as a template to select isolated teachings of the cited references and to modify and combine them without regard to what each of the references teaches as a whole. This exercise is improper:

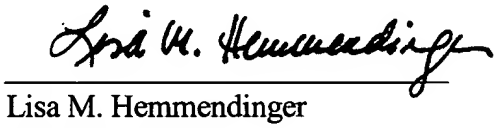
> [s]tatements [in a prior art reference] cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

The teachings of the cited references do not render claims 28-31 and 51-55 *prima facie* of obvious. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
BANNER & WITCOFF, LTD.

January 11, 2006

By: 

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